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201-14964

HIGH PRODUCTION VOLUME (HPV)

CHEMICALS CHALLENGE PROGRAM

PRELIMINARY TEST PLAN

For

CHLOROMETHYL METHYL ETHER

CAS NO. 107-30-2

Prepared by:

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EXECUTE SUMMARY

The Dow Chemical Company voluntarily submits the following screening information data and Preliminary Test Plan covering the chemical Chloromethyl Methyl Ether, also known as CMME (CAS No. 107-30-2), for review under the Environmental Protection Agency's High Production Volume (HPV) Chemicals Challenge Program. The Dow Chemical Company is in the process of forming a consortia with other producers to better document the uses and exposure conditions for this chemical. Thus this submission is considered to be incomplete. Dow Chemical expects the consortia to finalize the test plan and submit the finalized documents for the US HPV program.

A substantial amount of data exists to evaluate the potential hazards associated with CMME. Use of key studies or estimation models available from data already developed provide adequate support to characterize all but five endpoints in the HPV Chemicals Challenge Program. The five endpoints for which no data presently exists are aquatic toxicity, fish, daphne and algae, reproduction and developmental toxicity.

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TEST PLAN FOR CHLOROMETHYL METHYL ETHER

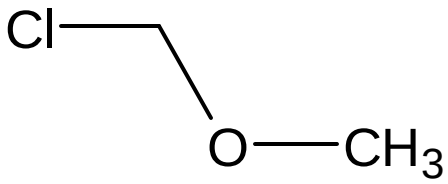
CAS Nos. 107-30-2

I. INTRODUCTION AND IDENTIFICATION OF CHEMICAL

Under EPA's High Production Volume (HPV) Chemicals Challenge Program, The Dow Chemical Company (Dow) has committed to voluntarily compile basic screening data on Chloromethyl Methyl Ether (CMME). The data included in this Test Plan provide physicochemical properties, environmental fate, and human and environmental effects of CMME, as defined by the Organization for Economic Cooperation and Development (OECD). The information provided comes from existing data developed by or on behalf of Dow or found in the published scientific literature.

A. Structure and Nomenclature

Following is a structural characterization of CMME and associated nomenclature.



Chloromethyl Methyl Ether
CAS No. : 107-30-2
Synonyms: CMME

B. Manufacturing & Use

To be supplied by the consortia that is being formed.

II. TEST PLAN RATIONALE

The information obtained and included to support this Test Plan have come from either:
1) Internal studies conducted by/or for Dow
2) Studies that have been extracted from the scientific literature either as primary references or as found in well-accepted, peer-reviewed reference books, or
3) Studies that were estimated using environmental models accepted by the US EPA (1999b) for such purposes.

This assessment includes information on physicochemical properties, environmental fate, and human and environmental effects associated with CMME. The data used to support this program include those Endpoints identified by the US EPA (1998); key studies have been identified for each data Endpoint and summarized in Robust Summary form and included in Section VII. of this Dossier.

All studies were reviewed and assessed for reliability according to standards specified by Klimisch *et al* (1997), as recommended by the US EPA (1999a). The following criteria were used for codification:
1. Valid without Restriction - Includes studies which comply with US EPA and/or OECD-accepted testing guidelines, which were conducted using Good Laboratory Practices (GLPs) and for which test parameters are complete and well documented,
2. Valid with Restrictions – Includes studies which were conducted according to national/international testing guidance and are well documented. May include studies conducted prior to establishment of testing standards or GLPs but meet the test parameters and data documentation of subsequent guidance; also includes studies with test parameters which are well documented and scientifically valid but vary slightly from current testing guidance. Also included were physical-chemical property data obtained from reference handbooks as well as environmental endpoint values obtained from an accepted method of estimation (i.e. EPIWIN).
3. Not Valid – Includes studies in which there are interferences in either the study design or results that provide scientific uncertainty or where documentation is insufficient.
4. Not Assignable – Includes studies in which limited data is provided.

Those studies receiving a Klimisch rating of 1 or 2 are considered adequate to support data assessment needs in this Dossier. In one case a positive response was reported for the Ames test and this study was assigned a Klimisch rating of 4. Given the supporting data available, this study was used for one end point in the HPV program.

III. TEST PLAN SUMMARY AND CONCLUSIONS

Physical-chemical property values (Melting Point, Boiling Point and Vapor Pressure) were considered to be acceptable.

Environmental Fate values for Transport (Fugacity) and Photodegradation were obtained using computer estimation –modeling programs. Biodegradation and Hydrolysis data were considered to be acceptable. The half-life of CMME in water is less than one second at 25C and pH 7.

Ecotoxicity studies have not been conducted in aquatic organisms. CMME is rapidly hydrolyzed to HCl, methanol and formaldehyde. Aquatic toxicity studies in fish, daphnia and algae are available for each hydrolysis product with the exception of an algae study with HCl. However, HCl toxicity for algae is most likely associated with pH changes and thus additional studies are unnecessary.

Mammalian Toxicity Endpoints (Acute Toxicity, Repeated Dose Toxicity, Ames Mutagenicity and Chromosomal Aberration Testing) have all been considered adequate.
A tabular depiction of data availability and testing recommendations for Chloromethyl Methyl Ether (CMME) can be found in Table 1.

IV. DATA SET SUMMARY AND EVALUATION

The key studies used in this assessment to fulfill the HPV requirements have been placed in an Endpoint-specific matrix, and further discussed below. Robust Summaries for each study referenced can be found in Section VII of this dossier.

A. Chemical/Physical Properties

All measureable HPV Endpoints for Chemical/Physical Properties have been completed (Table 2). At room temperature, CMME is a liquid with a vapor pressure of 286.6 hPa@25 C. Thus, a saturated atmosphere contains approximately 280,000 ppm CMME.

B. Environmental Fate and Biodegradation

All HPV Endpoints for Environmental Fate have been completed (Table 3). CMME is a very reactive molecule when dissolved in water (Table 2). The half-life of CMME in water is reportedly less than one second at 25^{o}C and pH 7. At a concentration of <50% (limited details available) the half life was less than 2 minutes.

However, the reaction in humidified air appears to occur at a much slower rate. As shown by Tou and Kallos (1974), the reaction appears to be a surface-catalyzed reaction since there was a greater than 10-fold difference in hydrolysis depending upon the material used for the reaction vessel. At a pH of 7, the half-life is approximately 224 hours. At a pH of 1.2, the half-life is 8.6 hours. The higher the relative humidity of air, the more rapid the hydrolysis.

It is readily biodegradeable in a MITI 1 biodegradation study.

C. Aquatic Toxicity

There is no aquatic toxicity data available for CMME (Table 4). As previously mentioned the rate of hydrolysis for CMME is extremely rapid with a half life at pH 7 and 25C of less than 1 second.

D. Mammalian Toxicity Endpoints

A summary of available toxicity data used to fulfill the HPV Endpoints for Mammalian Toxicity is found in Table 5. Each report has been further summarized in the Robust Summary section of this Dossier.

1.0 Acute Toxicity

The acute oral and dermal LD50s are 223 mg/kg and 300 mg/kg, respectively. The 7 hour LC50 is 55 ppm. The material is corrosive to the skin and eyes.

Thus based on the LD50 values, CMME would be considered moderate in toxicity. Due in part to the corrosive nature of CMME, protective equipment is required whenever contact with CMME is possible.

2.0 Repeated Dose Toxicity

A 30 day inhalation study was conducted at 1 and 10 ppm which demonstrated effects in the respiratory tract. At 10 ppm, approximately half of the CMME was degraded in the chamber.

In addition, carcinogenicity studies have been conducted in rats, mice and hamsters as well as epidemiology studies in humans. An increased incidence of pulmonary tumors was observed in mice exposed to CMME. The data is less conclusive for rats and hamsters. In a skin-painting study in mice, CMME acted as an initiator when followed by phorbol ester as the promotor. In several epidemiology studies, an increased incidence of lung cancer was observed in workers exposed to CMME.

3.0 Developmental Toxicity
There is no available developmental toxicity study (Table 6).

4.0 Reproductive Toxicity
There is no available reproduction toxicity study (Table 6).

5.0 Mutagenicity and Chromosomal Aberrations
5.1 Mutagenicity Testing (Ames test)
There is one study referenced in the literature which states that CMME was positive in the Ames test. Unfortunately, no additional information was provided and therefore it is rated a 4 in the Klimisch code.

5.2 - Chromosomal Aberrations
CMME was positive in the single in vitro study conducted and ambiguous in the single in vivo study conducted.

V. REFERENCES
ACGIH TLV (2002). Threshold Limit Values for chemical substances and physical agents and Biological Exposure Indices. American Conference of Governmental Industrial Hygienists.

Klimisch, H.-J., Andreae, M. and Tillman, U. 1997. A systematic approach for evaluating the quality of experimental toxicological and ecotoxicological data. Regul. Toxicol. Pharmacol. 25:1-5.

US EPA, 1998. Guidance for meeting the SIDS requirements (The SIDS Guide).
Guidance for the HPV Challenge Program (11/31/98).

US EPA, 1999a. Determining the adequacy of existing data. Guidance for the HPV
Challenge Program (2/10/99).

US EPA, 1999b. The use of structure-activity relationships (SAR) in the High Production Volume Chemicals Challenge Program. OPPT, EPA.

VI. ROBUST STUDY SUMMARIES -IUCLID
Data Sets are appended

Table 1. Test Plan Matrix for CHLOROMETHYL METHYL ETHER

	Info available?	OECD?	GLP?	Other study?	Estimated method?	Acceptable?
PHYSICAL CHEMICAL						
Melting Point	Y	R	R	N	N	Y, 2
Boiling Point	Y	R	R	N	N	Y, 2
Vapor Pressure	Y	R	R	N	N	Y, 2
Partition Coefficent	N	-	-	N	N	-
Water Solubility	N	-	-	N	N	-
ENVIRONMENTAL FATE ENDPOINTS						
Photodegradation	Y	N	N	N	Y	Y
Biodegradation	Y	Y	ND	N	N	Y
Transport between Environmental Compartmenats (Fugacity)	N	N	N	N	N	Y
Bioaccumulation	N	N	N	N	N	N
ECOTOXICITY						
Acute Toxicity to Fish	N	-	-	N	N	Y, data on degradation products
Acute Toxicity to Aquatic Invertebrates	N	-	-	N	N	Y, data on degradation products
Acute Toxicity to Aquatic Plants	N	-	-	N	N	Y, data on degradation products
MAMMALIAN TOXICITY						
Acute Toxicity	Y	N	N	N	N	Y
Repeated Dose Toxicity	Y	N	N	N	N	Y
Genetic Toxicity - Mutation (Ames)	Y	N	N	N	N	Y
Genetic Toxicity - Chromosomal Aberrations	Y	N	N	N	N	Y
Developmental Toxicity	N	-	-	-	N	-
Reproductive Toxicity	N	-	-	-	N	-

Y = Yes; N = No; S = Supplemental, not required under HPV; - = Not applicable

Table 2. Matrix of Available and Adequate Data on Chloromethyl Methyl Ether Physicochemical Properties

Name (CAS No.)	Melting Point (°C)	Vapor Pressure (hPa @ 25°C)	Boiling Point (°C)	Partition Coefficient (log Kow)	Water Solubility (mg/L @ 20C)
Chloromethyl methyl ether (CMME) (107-30-2)	-103.5 (measured)	162.7hPa@20C 286.6 hPa@25C (measured)	59 (measured)	-0.21 (estimated) not relevant since material is rapidly hydrolyzed	Not relevant since half life for hydrolysis is <1 second

Table 3. Matrix of Available and Adequate Data on Chloromethyl Methyl Ether Environmental Fate

Name (CAS No.)	**Hydrolysis**	**Photodegradation** Half life	**Biodegradation**	**Environmental Transport** Level III 1000 kg/hr released to air, water and soil
Chloromethyl methyl ether (CMME) (107-30-2)	Half life <1 second at 25C and pH 7	0.004 - 3.9 days	>80% in a MITI 1 study readily biodegradable	Not relevant since half life for hydrolysis is <1 second in water

Table 4. Matrix of Available and Adequate Data on Chloromethyl Methyl Ether Ecotoxicity

Name (CAS No.)	Acute Fish 96-hour LC50 (mg/l)	Acute Invertebrate 48-hour EC50 (mg/l)	Algal 72-hour growth inhibition EC50 (mg/l)
Chloromethyl methyl ether (CMME) (107-30-2)	No data Available data on hydrolysis products HCl - gambusia affinis - 282 mg/L Methanol - Lepomis macrochirus - 15,400 mg/L Formaldehyde - Ictalurus melas - 24.8 mg/L	No data Available data on hydrolysis products HCL - Daphnia magna - 72 hr EC50 - 56 mg/L Methanol - Daphnia species - 10,000 mg/L Formaldehyde - Daphnia magna - 2 mg/L	No data Available data on hydrolysis products HCl - Most likely unaffected at pH 5-10 Methanol - Microcystis aeruginosa - 7 day EC0 - 530 mg/L Formadelhyde - Scenedesmus quadricauda - 8 day TGK - 2.5 mg/L

Table 5. Matrix of Available and Adequate Data on Chloromethyl Methyl Ether Acute Toxicity

Name (CAS No.)	Acute Oral	Acute Dermal	Acute Inhalation	Dermal Irritation	Eye Irritation	Sensitization
Chloromethyl methyl ether (CMME) (107-30-2)	≥223 mg/kg	300 mg/kg	55 ppm for 7 hour exposure	Corrosive	Corrosive	No data

Table 6. Matrix of Available and Adequate Data on Chloromethyl Methyl Ether Repeat-dose Toxicity

Name (CAS No.)	Repeat Dose	Carcinogenicity	Reproductive	Developmental
Chloromethyl methyl ether (CMME) (107-30-2)	30 day study at 1 and 10 ppm	Positive in rats and humans	No data	No data

Table 7. Matrix of Available and Adequate Data on Chloromethyl Methyl Ether Genotoxicity

Name (CAS No.)	Genotoxicity (*in vitro* -bacterial)	Genotoxicity (*in vitro* - mammalian)	Genotoxicity (*in vivo*)
Chloromethyl methyl ether (CMME) (107-30-2)	Positive based on limited data and results from animal bioassay	Positive in DNA chromosomal aberration test	Ambiguous in mouse micronucleus assay

Table 8
Test Plan Matrix for Chloromethyl Methyl Ether

	CMME (107-30-2)
PHYSICAL CHEMISTRY	
Melting point, °C	-103.5 (measured) A
Boiling point, °C	59 (measured) A
Vapor Pressure, hPa at 25C	286.6 (measured) A
Water Solubility	Not relevant since half life for hydrolysis is <1 second NA
K_{ow}	Not relevant since half life for hydrolysis is <1 second NA
ENVIRONMENTAL FATE	
Biodegradation	>80% in a MITI 1 study Readily biodegradable A
Hydrolysis	Half life <1 second at 25C and pH 7 A
Photodegradability	 A
Transport between Environmental Compartments: (**Fugacity Level III Model**) Default assumption: 1000 kg/hr released into air, water, and soil.	
ECOTOXICITY	
Acute Toxicity to Fish (96hr LC50)	No data A due to rapid hydrolysis
Acute Toxicity to Aquatic Invertebrates (48hr EC50)	No data A due to rapid hydrolysis
Toxicity to Aquatic Plants (72hr EC50)	No data A due to rapid hydrolysis
TOXICOLOGICAL DATA	
Acute Toxicity (oral), mg/kg	≥223 mg/kg A
Acute Toxicity (dermal) mg/kg	300 mg/kg A

Acute Toxicity (inhalation)	55 ppm for 7 hour exposure A
Acute Eye Irritation	Corrosive A
Acute Skin Irritation	Corrosive A
Sensitization	No data NR
Repeated Dose Toxicity	30 day study A
Genetic Toxicity-Mutation	Positive A
Genetic Toxicity- Chromosomal Aberrations	Positive A
Toxicity to Reproduction	No data
Developmental Toxicity	No data

Legend	
Symbol	**Description**
R	Endpoint requirement fulfilled using category approach, SAR
Test	Endpoint requirements to be fulfilled with testing
Calc	Endpoint requirement fulfilled based on calculated data
A	Endpoint requirement fulfilled with adequate existing data
NR	Not required per the OECD SIDS guidance
NA	Not applicable due to physical/chemical properties